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EXAMINER	
SKIBINSKY, ANNA	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/685,737	RUBIN ET AL.	
	Examiner	Art Unit	
	Anna Skibinsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Applicant's

Applicant's amendments to claim 40 are acknowledged. Claims 40-43 are under examination.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 40-43 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-6 of U.S. Patent No. 6,759,206. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are either species of the instant claims of have only minor differences encompassed by the instant generic claims.

3. The instant claims are to a machine readable medium which automates the carrying out a process to measure the internalization of cell surface receptors while claims 1, 4-6 in U.S. Patent No. 6,759,206 are to and automated method that modulates internalization of cell surface receptor proteins. The instant claims recite a process that is generic to that of U.S. Patent No. 6,759,206, which is earlier filed. Further, though the instant application recites a machine readable storage medium that caries out a similar process of that in 6,759,206, it is obvious to automate a method according to MPEP 2144, Section III *In re Venner*. Thus, this constitutes an obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 40-43 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 40-43 are drawn to a a machine readable storage medium comprising the carrying out of a procedure for measuring internalized cell surface receptor proteins. The process involves the application of algorithms and calculations in claim 40 steps (a) and (b) that results in calculation of the of a measure of internalization of the cell surface receptor and, therefore, involves the application of a judicial exception. Regarding inventions involving the application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result . Furthermore, the claim must be limited only to statutory embodiments.

Claims 40-43 do not produce a tangible result. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the method is outputted to a display, a user, a readily accessible memory or other computer on a network, or by including a physical transformation.

Response to Arguments

Applicant's arguments filed 11/27/2006 have been fully considered but they are not persuasive.

Applicants argue the execution of procedures (claim 40, line 2) and causing a cell screening system to execute procedures (Remarks, page 12) is statutory subject matter.

In response, the instant claims are directed to the application of a judicial exception without involving a practical application of the judicial exception, meaning a real world result from the calculation, that is "useful, concrete, and tangible." Applicant's amendment directed to step (c), "displaying data on internalized cell surface receptor proteins," does not overcome the instant rejection because this limitation is not a practical application of the process steps (a) and (b). Rather, step (c) embodies the limitation of displaying any data on internalized cell surface receptor proteins. An amended claim 1, step (c) displays a calculated number or percent of internalized cells or a measure of internalization of the cell surface receptor proteins would be sufficient to overcome the instant rejection.

Claim Rejections - 35 USC § 112-1st paragraph

The rejection of claim(s) 40-43for New Matter under 35 USC § 112-1st paragraph in the Office Action filed 5/04/2006 is withdrawn in view of Applicant's Remarks/Amendments filed 11/27/2006

Claim Rejections - 35 USC § 112

The rejection of claim(s) 40-43 for being Vague and Indefinite under 35 USC § 112-2nd paragraph in the Office Action filed 5/04/2006 is withdrawn in view of Applicant's Remarks/Amendments filed 11/27/2006.

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. The instant claim recites "wherein the imaging multiple cells," (claim 43, lines 2-3). There is insufficient antecedent basis for this limitation in the claim. For the purpose of examination, this will be interpreted as "where in an imaging of multiple cells."

4. It is confusing as to whether the "to identify" in step (i) intends to recite an initial identifying step, using low resolution imaging, prior to a second step (ii) where a high resolution image is obtained or if both steps (i) and (ii) are directed to obtaining both high and low resolution images of locations in the array that contain cell surface receptor proteins. For the purpose of examination, the "obtaining a low resolution image

to identify locations" of part (i) will be interpreted as both "obtaining a low resolution image of locations" and "obtaining a low resolution image to first identify locations." Clarification is requested.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 40-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Marks et al. (US Patent 6,794,128).

The instant claims are drawn to a machine readable storage medium comprising a program containing instructions for measuring internalization of cell surface proteins through a cell screening system.

2. Claim 40 recites identifying internalized cell surface receptor proteins in cells where individual cells comprise at least a first luminescent reporter molecule that reports on the cell surface receptor and at least a second luminescent reporter molecule that reports on cells. Identifying internalized cell surface receptors by determining a luminescent signal from the first reporter molecule that surpasses a user defined intensity.

3. Marks et al. teach a method of internalizing phages into target cells and identifying the internalized phages (Abstract). The prior art provides embodies providing methods of identifying internalizing antibodies and internalizing receptor

ligands (col. 1, lines 20-26, col. 3, lines 17-25). This includes identifying internalizing antibodies as well as internalizing receptors (col. 1, lines 20-25). The method can be carried out by labeling the phage with a reporter gene encoding a fluorescent protein such as GFP or a luciferase (col. 2, line 66 to col. 3, line 5; and col. 4, lines 9-12).

4. Marks et al. teaches a method of identifying internalized receptors.(col. 13, lines 44-55) as well as using reporter genes to identify cells that express GFP. This method can be used to identify target cells (col. 17, line 45 to col. 18, line 22) within a subtractive cell line (col. 18, lines 23-65). Here, the subtractive cells display all the markers of the target cell except the marker (e.g. receptor) that is to act as a target for the desired binding of antibodies or binding polypeptides. This reads on the limitations set forth in claim 40(a) where each cell is contacted with at least two reporter molecules.

5. Marks et al. goes on to teach identification of an internalized phage (col. 19, line 57 to col. 20, line 10) with the use of a detectable fluorescent signal where the phage bears a marker (e.g. label) and the surface bound or internalized phages are sorted (col. 20, lines 3-14).

6. The prior art of Marks et al. teaches the measuring of internalized phages with FAC (fluorescence activated cell sorting) and expressed in MFI or percent of positively fluorescing cells (col. 46, lines 47-48; col. 47, line 65 to col. 48, line 3; and Figure 9). This reads on the limitations set forth in claim 40(b) where calculations provide a measurement of the internalization of the cell surface receptor in individual cells.

7. Claim 40, step (c) recites displaying data on internalized cell surface receptor proteins.

8. Marks et al. teaches a table containing data on cell surface bound phage and internalized phage (col. 29, Table 4).

9. Claim 41 recites the steps (a) and (b) carried out at multiple time points. As illustrated in Figure 9, the internalization of the phages are calculated at multiple time points.

10. Claim 42 recites determining an aggregate area of the objects that represent the internalized cell surface receptor protein (step (i)) and a number of objects that represent the internalized cell surface receptor protein (step (iv)).

11. Marks teaches that the methods of the prior art invention can be used to identify internalizing receptors and regions of the receptor that when bound induce internalization of the binding moiety (col. 3, lines 17-20), as in claim 41, step (i). Marks further teaches the identifying of internalized members of the phage display library if the members are internalized into one or more of the target cells (col. 3, lines 38-40).

RESPONSE TO ARGUMENTS

12. Applicant's arguments filed 11/27/2006 have been fully considered but they are not persuasive.

13. Applicants argue (Remarks, page 5, lines 1-3) that Marks does not teach labeling of antibodies or bacteriophage or polypeptides that are not cell surface receptor proteins and assessing their internalization by fluorescence microscopy.

14. Marks does teach assessing internalization by fluorescence microscopy, as reiterated in the above rejection. Marks teaches identifying internalizing antibodies as

well as internalizing receptors (col. 1, lines 20-25). The method can be carried out by labeling the phage with a reporter gene encoding a fluorescent protein such as GFP or a luciferase (col. 2, line 66 to col. 3, line 5; and col. 4, lines 9-12).

15. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., assessing internalization by fluorescence microscopy) are not recited in the rejected claim(s).

16. Applicants argue (Remarks, page 5, lines 3-4) that Marks does not teach methods for identifying internalizing receptors.

17. In response, Marks does teach identifying internalizing receptors (col. 13, lines 44-55) where Marks recites "Once an antibody of polypeptide that is internalized into a cell has been identified," which directly reads on the limitation of claim 40 reciting "identifying internalized cell surface receptor proteins in multiple individual cells." Further, Marks explicitly states that the instant prior art "provides methods for identifying internalizing antibodies and internalizing receptor ligands, as well as the internalizing receptors bound," (col. 1, lines 20-26).

18. Applicants argue (Remarks, page 5, line 18) that the teachings of Marks are "quite distinct from the presently claimed invention."

19. In response, applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections

made. Further, they do not show how the amendments avoid such references or objections.

20. Applicants argue (Remarks page 5, lines 24-26) that Marks teaches expression of GFP-antibody chimeric protein in cells and not a measure of cell surface receptor protein internalization.

21. In response, the limitation of claim 40, step (b) to which this refers recites calculating a number/or percentage of individual cells that internalized the labeled reporter molecule. Marks teaches that the cells were analyzed for GFP expression and the MFI which is the mean fluorescent index (col. 46, lines 47-48 ;col. 47, line 65 to col. 48, line 3; and Figure 9) in reference to cells that had internalized phage particles (col. 45, lines 32-34). Figures 9 (a)-(d) show phage concentrations in cells and the MFI of fluorescing cells expressing GFP which reads on the limitation of being an internalized luminescent reporter molecule. The Abstract of Marks additionally teaches that "target cells are cultured under conditions where members of the phage display library can be internalized if bound to an internalizing marker and internalized members of the phage display library are then identified."

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 40-43 rejected under 35 U.S.C. 103(a) as being unpatentable over Marks as applied to claims 40-42 above, and further in view of Dunlay et al. (US Patent 5,989,835, in IDS filed 5/19/04).

4. Marks et al. teach the identification of internalized receptors wherein the cells contain internalized green fluorescent proteins that reports on cells that contain the internalized receptors. Internalizing antibodies in an affinity matrix or solid support at taught (col. 13, lines 56-62) as required by claims 40-42. However, Mark does not teach the images of the array to obtain both low and high resolution images of those array locations that contain internalized cell surface receptor proteins.

5. Dunlay et al. teach providing cells containing fluorescent reporter molecules in an array of locations and scanning numerous cells in each location with a fluorescent microscope (Abstract). The whole area of the plate can be imaged (col. 1, lines 32-37) where cells have been treated with fluorescent reagents such as GFP and expressing GFP in cells for use as reporter molecules (col. 2, lines 11-53). Further Dunlay et al.

teach imaging the array of cells at a low resolution and imaging particular locations in the microplate at a higher resolution (col. 5, lines 19-27).

6. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented imaging technique of Dunlay et al. to image the cells with internalized GFP reporter molecules that report on internalized receptors as taught by Marks. One of skill in the art would have been motivated to use the multi-resolution imaging technique of Dunlay et al. because Dunlay et al teach that using two resolution improves the overall throughput of the screening system (col. 4, lines 25-27).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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